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EXAMINER
SCHWADRON, R

18N1/1127

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1816	22

DATE MAILED: 11/27/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/21/95 (8/25/95) ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9, 11-16, 19-21 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 10, 17, 18 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-9, 11-16, 19-21 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. Claims 1-9,11-16,19-21 are under consideration. Claim 18 has been cancelled. Claims 1,8,14 and 19 have been amended.

RESPONSE TO APPLICANTS ARGUMENTS

16. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to for the reasons discussed in paragraph 20 of the Office Action mailed 4/17/95.

17. Claims 1-9,11-16,19 and newly added claims 20 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicant has not shown how to use the instant invention for the treatment of microvascular bleeding in vivo in humans. The claims of the instant invention read on a method of treating humans or a composition for treating humans. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. The state of the art is such that is unpredictable

from the animal data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of microvascular bleeding in vivo in humans. With regards to the pig model used in the experiments disclosed in the specification, Montagna et al. teach that pig skin is not an appropriate model for human skin. Montagna et al. teaches that:

"This study makes it clear that in spite of a few similarities, the dissimilarities in morphologic and histochemical attributes of the skin of the pig and that of man are considerable. In light of this, we should all reflect soberly in the future before uttering again the fantasy that the skin of the pig resembles more that of man than that of any other mammal. To seek a skin similar to that of man, consideration should be given to the anthropoid primates, and particularly, the apes." (page 20, second column, last paragraph).

Furthermore, applicant discloses in the specification that:

"Although the short and long term effects of creating a pharmacologically induced transient hypercoagulable state needs further study prior to widespread clinical use, these preliminary data suggest it to be free of short term complications in a porcine model."(page 21, penultimate paragraph).

This statement seems to indicate that even applicant acknowledges that the pig model is not necessarily predictive of what will occur when the instant invention is administered to humans. Chesebro et al. teach that, "Thus, dose activity responses in vivo are needed first in animals and then in humans before clinical efficacy trials are initiated."(page 101, second column, last complete sentence), indicating that Chesebro et al. believe that animal data in itself is an inadequately predictive as to whether a particular therapy can be used in humans for the treatment of disease.

With regards to the in vivo use of antibodies against protein C in humans, Waldmann teaches that the therapeutic use of antibody treatment with any particular antibody in humans is unpredictable

from animal data alone. Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). Waldmann also states that results from clinical studies in humans using antibody based therapeutics for the treatment of cancer did not fulfill the hopes engendered by animal studies (see page 1660, second column, last paragraph). Waldmann teaches that the effectiveness of rodent monoclonal antibodies is limited because they "have a short survival time in humans and induce an immune response that neutralizes their therapeutic effect"(page 1658, second column, third paragraph). Waldmann teaches that even human antibodies can be immunogenic by virtue of their idiotypic elements(see page 1659, first column, lines 4 and 5). Harris et al. teach that, "There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy" and goes on to list problems encountered upon the use of murine antibodies for human therapy (see page 42, second column, first paragraph). Harris et al. also states that, "However, the residual HAMA response to chimaeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective" (see page 42, third column).

With regards to the use of inhibitors of an anticoagulant other than the HPC-4 anti-protein C antibody, the specification discloses that, "the possibility of pathologic thrombosis must certainly be considered whenever a systemic thrombogenic drug is utilized"(page 14, last paragraph). While the specification provides evidence that this does not occur in the pig model when HPC-4 anti-protein C antibody is used, there is no disclosure in the specification as to whether other inhibitors of an anticoagulant encompassed by the claims would cause pathologic thrombosis when administered in vivo (even in the pig model), thus precluding the use of said agents in

vivo in humans. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Regarding applicants comments in the amendment received 8/21/85, applicants arguments have been considered and deemed not persuasive. Regarding applicants comments on page 6, last paragraph of the instant amendment, the specification discloses that "the possibility of pathologic thrombosis must certainly be considered whenever a systemic thrombogenic drug is utilized"(page 14, last paragraph). While the specification provides evidence that this does not occur in the pig model when HPC-4 anti-protein C antibody is used, there is no disclosure in the specification as to whether other inhibitors of an anticoagulant encompassed by the claims would cause pathologic thrombosis when administered in vivo (even in the pig model), thus precluding the use of said agents in vivo in humans. Regarding the Esmon et al. patent 5,147,638, there is no evidence presented in said patent with regards to the use of the method of the instant invention in humans. Regarding applicants comments on page 8 of the instant amendment, ONCOSCINT CR/OV is approved for the diagnosis of cancer in humans. None of the claims of the instant invention read on the diagnosis of cancer. ONCOSCINT CR/OV is not approved for the treatment of human disease. DIGIBIND is used for acute digoxin intoxication. None of the claims of the instant invention read on a method of treating acute toxicity related to digoxin. Regarding other publications cited by applicant on page 8 of the instant amendment, no evidence has been presented indicating that antibodies can be used as per the method of the instant invention for the treatment of human disease. Regarding applicants comments on page 8, only one monoclonal antibody is currently approved for the treatment of human disease (OKT3). While other antibodies may currently be in phase III trials, the reasons said antibodies are in phase III trials is because the efficacy of said antibodies for the treatment of human disease has not been

established. With respect to applicant's print out listing 1308 titles, it is unclear as to why this compilation of titles establishes that murine antibodies can be used for the treatment of human disease. With regards to the use of monoclonal antibodies in humans, Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). The fact that only one murine antibody has been approved for clinical use in view of widespread attempts to use antibodies therapeutically, confirms the comments expressed by Harris et al. and Waldmann. Regarding the Squires et al. publication, there is no evidence in said publication indicating that the method of the instant invention can be used for the treatment of human disease. With regards to the pig model used in the experiments disclosed in the specification, Montagna et al. teach that pig skin is not an appropriate model for human skin. Montagna et al. teaches that:

"This study makes it clear that in spite of a few similarities, the dissimilarities in morphologic and histochemical attributes of the skin of the pig and that of man are considerable. In light of this, we should all reflect soberly in the future before uttering again the fantasy that the skin of the pig resembles more that of man than that of any other mammal. To seek a skin similar to that of man, consideration should be given to the anthropoid primates, and particularly, the apes." (page 20, second column, last paragraph). In the amendment received 5/4/94, page 4, applicant indicates that Montagana et al. establishes the state of the art with regards to the relation of the pig model to human disease. Applicant discloses in the specification that:

"Although the short and long term effects of creating a pharmacologically induced transient hypercoagulable state needs further study prior to widespread clinical use, these preliminary

data suggest it to be free of short term complications in a porcine model."(page 21, penultimate paragraph).
This statement seems to indicate that even applicant acknowledges that the pig model is not necessarily predictive of what will occur when the instant invention is administered to humans.

18. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to for the reasons discussed in paragraph 24 of the Office Action mailed 4/17/95.

19. Claims 4 and 19 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. Applicant has provided insufficient guidance in the specification with respect to the topical administration of an inhibitor of a natural anticoagulant of the instant invention. There is no guidance in the specification as to dosage or particular time when the inhibitor of an anticoagulant would be administered topically. It is also unclear as to whether topical administration will result in the absorption of sufficient quantities of the instant invention to achieve sufficient inhibition of protein C that is constantly arriving at the site of microvascular bleeding via influx of blood. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). It is unclear as to whether the administration of said antibody when administered topically to a bleeding site where activated protein C is present would have any effect on microvascular bleeding. Activated protein C is innately present at the site of bleeding because it is involved in the mechanism whereby bleeding occurs. It appears that

undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. Applicant has not addressed the issues raised in said rejection in the amendment received 8/21/95.

20. Claims 1-9,11-16,19 and newly added claim 20 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the use of the HPC-4 antibody in the method of the instant invention in pigs(or composition containing said antibody) for the reasons detailed in paragraph 25 of the previous Office Action. Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including $CA^{2}+$ dependency (see column 2, last paragraph). It is not apparent that any antibody per se against protein C would be able to mediate the microvascular bleeding inhibition effect achieved when this antibody with unique properties is used in pigs. In addition it is equally unclear whether nonantibody agents that inhibit protein C function would be able to mediate the effect seen using the HPC-4 antibody. In the specification it is recited that the agent used must inhibit, "greater than 90% of potential activated protein C in human plasma" (see specification, page 14, third paragraph). It is not disclosed in the specification whether other agents can achieve this degree of protein C inactivation as occurs with the unique HPC-4 antibody. The enablement is not commensurate with the scope of claims that read on any antiprotein C antibody or protein C inhibiting agent other than the HPC-4 antibody. See M.P.E.P. §§ 706.03(n) and 706.03(z).
Applicant has not addressed the issues raised in said rejection in the amendment received 8/21/95.

21. Claims 1-9,11-16,19 and newly added claims 20 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure

is enabling only for claims limited where the HPC-4 antibody is given prior to the initiation of microvascular bleeding as per the experiments depicted in pages 17-21 of the specification for the reasons detailed in paragraph 26 of the previous Office Action. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). It is therefore unclear as to whether the instant invention can be used to prevent microvascular bleeding after the bleeding has already occurred, because activated protein C is now present and the HPC-4 antibody does not bind to protein C once it is activated. There is no disclosure in the specification as to the efficacy of the instant antibody in treating microvascular bleeding when the antibody is administered after microvascular bleeding has occurred. All of the experiments described in the specification administered the HPC-4 antibody prior to the initiation of bleeding. Paragraph 25 of the instant Office Action establishes that the specification is only enabling for the use of HPC-4 in the instant invention. The enablement is not commensurate with the scope of claims that read on the use of the instant invention after microvascular bleeding is already established. See M.P.E.P. §§ 706.03(n) and 706.03(z). Applicant has not addressed the issues raised in said rejection in the amendment received 8/21/95.

22. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention

was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

23. Claims 1-3,7,11-13 and newly added claims 20 and 21 stand rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) for the reasons elaborated in paragraph 28 of the previous Office Action. Applicants arguments have been considered and deemed not persuasive. With regards to applicant's comments in the amendment received 8/21/95, Esmon et al. (US Patent 5,202,253) teaches that the antiprotein C antibody can be used to promote clotting, "in individuals where it is desirable to do so" (see paragraph four, column 12). It would have been obvious to a routineer that this statement referred to clotting at any anatomical site or location and was applicable to normal tissue. Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13). It would have been obvious to a routineer that microvascular bleeding in any anatomical location or site could be stopped by treatment with antiprotein c antibody. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed the method of the instant invention because Esmon et al teaches the HPC-4 antiprotein c antibody and the use of said antibody to promote clotting,Esmon et al. teaches the HPC-4 antibody in a pharmaceutically acceptable carrier, at a dosage to block greater than 90% of endogenous protein C , Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13) and a routineer would have realized that since the antiprotein

C antibody can be used to promote clotting, including clotting of the microvascular bed of a tumor, then the instant antibody could be used to promote microvascular clotting in any application that was desired. One of ordinary skill in the art would have been motivated to do the aforementioned to treat microvascular bleeding in disease states, in view of the teachings of Esmon et al. (US Patent 5,202,253) that the instant antibody can be used to promote clotting including clotting of the microvasculararature.

24. Claims 14-16 remain rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in paragraph 30 of the previous Office Action. Applicants arguments have been considered and deemed not persuasive. Claim 14 is still indefinite in that it is unclear as to whether the composition consists of two physically separate agents or two agents that are physically mixed together. If the language used is interpreted as including two agents mixed together, than there is no disclosure in the specification of such a composition. The specification (page 14, second paragraph) teaches that an inhibitor of a natural anticoagulant, when prepared for systemic administration is prepared with a liquid pharmaceutical carrier such as saline or phosphate buffered saline. The specification teaches that topically prepared agents are administered in powdered or lyophilized (freeze dried powder) form. Obviously, these two forms could not coexist in the same physical preparation. Furthermore, a composition containing thrombin could not be injected systemically due to the art known complications that arise from systemic injection of thrombin (eg. massive internal coagulation). Therefore the specification is not enabling for the instant invention.

25. Claims 1-9,11-13,19 and newly added claims 20 and 21 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "prevent anticoagulation" because it is unclear as to what this means or encompasses. If the term is interpreted as meaning preventing the generation of activated protein C in the plasma via preventing the generation of active protein C from inactive protein C, than there is support for this concept in the specification. However, if this term is interpreted as meaning preventing the action of the activated protein C, than said interpretation is not enabled by the specification under 35 U.S.C. § 112, first paragraph. The specification teaches on page 14, that the dosage to be administered is that required to block greater than 90% of "potential activated protein C", not protein C that has already been activated. Paragraph 25 of this Office Action establishes that the specification is enabling only for the use of the HPC-4 antibody in the instant invention. This antibody binds inactive protein C and prevents the activation of protein C, but does not bind activated protein C and therefore has no effect on the function of activated protein C. Therefore the specification is not enabling for the instant invention wherein the claim reads on an agent that can prevent the function of activated protein C.

26. Claims 4 remains rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13, 20 and 21 above (paragraph 23), and further in view of Nishimaki et al. (US Patent 5,130,244) as elaborated in paragraph 33 of the previous Office Action. Applicants arguments

have been considered and deemed not persuasive. Paragraph 23 of the instant Office Action makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant. Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery (see column 1, second paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed the method of the instant invention where the inhibitor of an anticoagulant is administered topically because paragraph 23 makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant and Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery. One of ordinary skill in the art would have been motivated to do so because Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery. One of ordinary skill in the art would have a reasonable expectation of success because paragraph 23 makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant and Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery.

27. Claims 5,6,8,9,14-16 and 19 remain rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13 above and Esmon et al. (US Patent 5,202,253) in view of Nishimaki et al. (US Patent 5,130,244) as applied to claims 4 and 18 above, and further in view of Furie et al. for the reasons elaborated in paragraph 34 of the previous Office Action. Applicants argument have been considered and deemed

not persuasive. Nishimaki et al. teach that thrombin (a coagulant) is used clinically as a topical agent to exert a blood coagulating effect (see column 1, paragraph 2). It would have been obvious to a routineer that thrombin could have used as a coagulant to treat any known form of bleeding, including microvascular bleeding. Furie et al. teach that clot formation (eg. clotting or coagulation) is mediated by thrombin via the effect of thrombin on fibrinogen (see page 505, column one, last paragraph, continued on column two). Furie et al. also teach that thrombin can also lead to the activation of protein C, which is an anticoagulant which would prevent blood clotting (see page 506, column two, last paragraph, continued on page 507). In a physiological setting, these two effects of thrombin interact to determine how much clotting occurs when thrombin is present at a site of bleeding. In view of the fact that the clotting ability of thrombin is negatively regulated by protein C, it would have been obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is a anticoagulant which counteracts the coagulant property of thrombin. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed either of the two permutations of the instant invention as described in paragraph one of this rejection because paragraph 23 makes obvious the method for inhibiting microvascular bleeding in a patient by blocking greater than 90% of activated protein C function with a compound that is an inhibitor of an anticoagulant (eg. antiprotein C antibody) and wherein said inhibitor is administered systemically, paragraph 26 makes obvious the topical administration of said inhibitor of an anticoagulant, Nishimaki et al. teach that thrombin (a coagulant) is used clinically as a topical agent to exert a blood coagulating effect and Furie et al. disclose that the clotting ability of thrombin is negatively regulated by protein C, and it would have been therefore

obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is an anticoagulant which counteracts the coagulant property of thrombin. One of ordinary skill in the art would have been motivated to do the aforementioned in order to increase the efficacy of thrombin to inhibit microvascular bleeding, in view of the teaching of Furie et al. that protein C was an anticoagulant generated by thrombin which negatively regulated the coagulation caused by thrombin, and the knowledge that antiprotein C antibody could inhibit anticoagulation mediated by protein C.

OTHER REJECTIONS

28. The following new grounds of rejection were necessitated by applicant's amended claims.

29. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

It is apparent that the hybridoma which secrets the antibody known as HPC-4 is required to practice the instant invention as recited in claim 21 which recites the respective antibody. As a required element, the hybridoma and cell line must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If said hybridoma and cell line are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the

instant hybridoma. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the hybridoma which secrets the antibody known as HPC-4. There is no disclosure in the specification of the particular epitope recognized by the antibody produced by said hybridoma and therefore a routineer would not be able to produce said hybridoma based on the disclosure of the specification. Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including $CA^{2}+$ dependency (see column 2, last paragraph). There is no disclosure in the specification as to how such an antibody would be made. In addition, the claim reads on a specific deposited hybridoma that would have specific properties of the particular clone or subclone that was deposited at the time of deposit. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.801-1.809 for additional explanation of these requirements.

While the aforementioned hybridoma has been deposited with the ATCC, applicants need to comply with all of the deposit requirements as per 37 CFR 1.801-1.809. Applicant needs to submit a statement with regards to the HPC-4 producing hybridoma indicating that, "All restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the US patent." (see 37 CFR 1.808). There is no indication that the HPC-4 producing hybridoma was deposited under conditions of the Budapest treaty, therefore applicants need to meet all requirements specified in 37 CFR 1.801-1.809 for cell lines not deposited under conditions of the Budapest treaty. Claim 21 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

30. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite in that it depends on cancelled claim 18.

31. No claim is allowed.

32. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

33. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7401.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00.

The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Margaret Parr can be reached on (703) 308-2454. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
Patent Examiner
Art Unit 1816
November 20, 1995

M. Parr 11/22/95

MARGARET PARR
SUPERVISOR PATENT EXAMINER
GROUP 1800